Remarks

This paper is responsive to the non-final Office Action mailed November 12, 2010. Claims 1-15 are pending in the instant application and claims 13-15 are withdrawn from consideration. In the Action, the Office rejected claims 1-12. Applicant hereby amends claims 1 and 3-5, and cancels claim 2 without prejudice or disclaimer.

Rejection – 35 U.S.C. § 102(b)

The Office has rejected claims 1 and 5 under 35 U.S.C. § 102(b) as being anticipated by Nagashima *et al.* (Blood, **1998**, *91*(*10*), 3850-3861). Claims 1 and 5 have been amended to recite that the packaging cell line is a Phoenix cell line. Applicant submits that the Phoenix cell line, which is derived from human embryonic kidney (HEK) cells, is both biologically and structurally distinct from the CRIP cell line employed by Nagashima, which is derived from mouse fibroblast cells. HEK cells are differentiated human kidney cells, while CRIP cells are derived from fibroblast. Further, Applicant submits that the chemical behavior of these cell lines will be different as they are not only from different organisms, but that the cell lines are from different physiological locations within their respective organisms.

Applicant submits that no prior art teaches that MuLV-based retroviral vectors are capable of successfully transfecting $CD56^{dim}$ NK cells. Therefore, one of ordinary skill in the art would not reasonably have anticipated experimental success with the MuLV-based retroviral vector taught by Nagashima. As it has not been demonstrated that the MuLV-based vector of Nagashima can transfect $CD56^{dim}$ NK cells, it would not be reasonable for one of skill in the art to anticipate the success of an unrelated retroviral vector [*e.g.*, an Epstein-Barr viral (EBV) vector] either. Applicant respectfully submits that for at least these reasons the claimed inventions are not anticipated, and respectfully requests withdrawal of the rejection.

Rejection – 35 U.S.C. § 103(a)

Claims 1-4 and 6 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Nagashima *et al.* (Blood, **1998**, *91*(*10*), 3850-3861) in view of Golay *et al.* (US 2007/0014785 A1). Applicant respectfully traverses the rejection.

Applicant respectfully submits that Nagashima *et al.* disclosed the transfection of human NK cells, specifically NK-92 and YT2C2 cell lines, with retroviral vectors derived from MuLV. However, no evidence has been provided by Nagashima suggesting that transfection of $CD56^{dim}$ NK cells with a PINCO vector, or any vector derived from Epstein-Barr virus (EBV) is possible.

The Office also asserts that Golay teaches "the use of PINCO retroviral vector and Phoenix-Ampho cells for transfection with the exogenous gene." Applicant respectfully submits that while Golay may teach the use of PINCO retroviral vector and Phoenix-Ampho cells, Golay also teaches that introduction of the exogenous gene is to T-lymphocytes, not NK cells or more precisely $CD56^{dim}$ NK cells. Although T-lymphocytes and NK cells are both lymphocytes, these cell are immunologically very different. T-lymphocytes mature in the thymus, play a central role in cell-mediated immunity, and are identified by the presence of T-cell antigen receptors (TCR) on the their surface. The surface immunochemistry (*e.g.*, TCR) of T-lymphocytes is responsible for the adaptive immune response, hence the binding of the T-lymphocyte to the antigen of the major histocompatibility complexes (MHC-I) of other cells. In contrast, NK cells are not processed by the thymus, are cytotoxic lymphocytes that trigger an innate immune response, and NK cells lack T-cell antigen receptors. Natural killer cells induce apoptosis in cells that lack "self" markers (*i.e.*, major histocompatibility complexes). For at least these reasons, Applicant submits that one of ordinary skill in the art reading Nagashima and Golay either individually or together would not find the claimed inventions obvious. Applicant respectfully submits that for at least these reasons the claimed inventions are not obvious, and respectfully requests withdrawal of the rejection.

Rejection – 35 U.S.C. § 103(a)

Claims 1 and 7-10 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Nagashima *et al.* (Blood, **1998**, *91(10)*, 3850-3861) in view of Fischer *et al.* (Exp. Clin. Cardiol. **2002**, *7(2/3)*, 106-112). Applicant respectfully traverses the rejection.

Applicant submits that Nagashima fails to teach the size of the transfected DNA or the maximum packaging capabilities of the CRIP cell line. Office asserts that Fischer teaches "[t]hat inserts up to 6 to 7 Kb were known to be useable in retroviral vectors." Applicant submits that

Fischer states "[B]y deleting these viral protein-coding regions from the genome, retroviruses are made replication defective and can offer a maximal packaging capability of 6 to 7 Kb (28)," which is dependent upon reference 28 (J. A. Levy, H. Fraenkel-Conrat, R. A. Owens; *Virology*, 3 Ed.: 1994, 129-133, 189-190) cited by Fischer. Upon careful examination of Levy, it is clear that the cited work covers the structure of retroviruses and components, and virus production (*i.e.,* the natural viral replication cycle, not engineered virus production). Levy, at no point in the text addresses deletion of viral protein-coding regions, replication deficiencies, or maximal packaging capabilities of retroviral vectors. Clearly, the claim made by Fischer with respect to maximal packaging capabilities of retroviral vectors (*e.g.*, 6 to 7 Kb) is not substantiated and therefore in light of Levy (the underlying reference) fails to serve as valid proof "[t]hat inserts up to 6 to 7 Kb were known to be useable in retroviral vectors." Applicant respectfully submits that for at least these reasons the claimed inventions are not obvious, and respectfully requests withdrawal of the rejection.

Rejection – 35 U.S.C. § 103(a)

Claims 11 and 12 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Nagashima *et al.* (Blood, **1998**, *91*(*10*), 3850-3861) in view of Campana *et al.* (US 2005/0113564 A1). Applicant respectfully traverses the rejection.

Applicant respectfully submits that the present method is believed to be the first to result in the transfection of the $CD56^{dim}$ population: other methods, including that of Nagashima, are effective at transfecting the $CD56^{bright}$ population only. Therefore, a method capable of transfecting both $CD56^{bright}$ and **$CD56^{dim}$** NK cell population subsets, which possess immunologically distinct functions, would be highly advantageous. Transfection of the $CD56^{dim}$ population subset using a PINCO vector was found to be highly unexpected as prior art using either MuLV or MSCV were only capable of transfecting the $CD56^{bright}$ population as reported by Nagashima and Campana, respectively. Further, the unexpected transfection of the $CD56^{dim}$ population would not have been obvious to one of ordinary skill in the art and therefore one of ordinary skill in the art would not have found it obvious to label (*e.g.*, attach a GFP or CD8 marker) the population subset that at the instant of application had not been taught to be capable

of transfection. Applicant respectfully submits that for at least these reasons the claimed inventions are not obvious, and respectfully requests withdrawal of the rejection.

In the event the Commissioner should decide that any additional fee or fee deficiency is due, the Commissioner is hereby authorized to charge any and all fees incurred as a result of entering or considering this document to deposit account number 03-0172.

Respectfully submitted,

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Date: April 11, 2011

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